

Patent claims

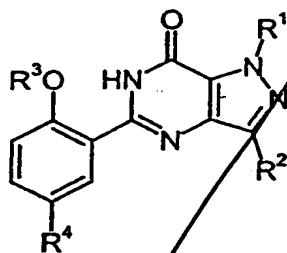
1. A combination preparation, comprising as pharmaceutically active ingredients at least one active compound component A and at least one active compound component B, characterized in that the active compound component A is a PDE inhibitor, preferably a cGMP PDE inhibitor, and the active compound component B is an antilipemic.
2. The combination preparation as claimed in claim 1 for treating sexual dysfunction in men or women.
3. The combination preparation as claimed in claim 2 for treating erectile dysfunction.
- 15 4. The combination preparation as claimed in any of claims 1 to 3, characterized in that the two active compound components A and B are used either simultaneously or successively.
- 20 *sub A/20* 5. The combination preparation as claimed in any of claims 1 to 4, characterized in that the active compound components A and B are present as a functional unit, in particular in the form of a mixture, a mix or a blend.
6. The combination preparation as claimed in any of claims 1 to 4, characterized in that the active compound components A and B are (spatially) separated, in particular as a kit-of-parts.
- 25 7. The combination preparation as claimed in any of claims 1 to 6, characterized in that the antilipemic (active compound component B) is selected from the group consisting of (a) HMG-CoA-reductase inhibitors; (b) squalene synthase inhibitors; (c) bile acid sequestrants; (d) fibrac acid and its derivatives; (e) nicotinic acid and its analogs; (f) ω 3-fatty acids.
- 30 8. The combination preparation as claimed in claim 7, characterized in that the

5 antilipemic (active compound component B) is an HMG-CoA-reductase inhibitor and is in particular selected from the group of the statins, preferably from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, itavastatin, simvastatin and (+)-(3R,5S)-bis-(7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-pyrimidin-5-yl)-3,5-dihydroxy-6(E)-heptenoic acid, and their respective salts, hydrates, alkoxides, esters and tautomers.

9. The combination preparation as claimed in claim 8, characterized in that the
10 antilipemic (active compound component B) is atorvastatin or its salt, hydrate, alkoxide, ester and tautomer.

10. The combination preparation as claimed in claim 8, characterized in that the
15 antilipemic (active compound component B) is cerivastatin or its salt, hydrate, alkoxide, ester and tautomer.

11. The combination preparation as claimed in any of claims 1 to 10, characterized in that the PDE inhibitor (active compound component A) is a cGMP PDE inhibitor and is in particular selected from the group consisting of pyrazolopyrimidones of the general formula below



in which

25 R¹ represents hydrogen; C₁-C₃-alkyl; C₁-C₃-perfluoroalkyl; or C₃-C₅-cycloalkyl;

R² denotes hydrogen; C₁-C₆-alkyl, optionally substituted by C₃-C₆-cycloalkyl; C₁-C₆-perfluoroalkyl; or C₃-C₆-cycloalkyl;

R³ is C₁-C₆-alkyl, optionally substituted by C₃-C₆-cycloalkyl; C₁-C₆-perfluoroalkyl, C₃-C₅-cycloalkyl; C₃-C₆-alkenyl; or C₃-C₆-alkinyl;

5 R^4 represents C_1 - C_4 -alkyl, optionally substituted by OH, NR^5R^6 , CN, $CONR^5R^6$ or CO_2R^7 ; C_2 - C_4 -alkenyl, optionally substituted by CN, $CONR^5R^6$ or CO_2R^7 ; C_2 - C_4 -alkanoyl, optionally substituted by NR^5R^6 ; (hydroxy)- C_2 - C_4 -alkyl, optionally substituted by NR^5R^6 , (C_2 - C_3 -alkoxy)- C_1 - C_2 -alkyl, optionally substituted by OH or NR^5R^6 , CO_2R^7 ; halogen; NR^5R^6 , $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl, each of which is optionally substituted by methyl;

10 R^5 and R^6 each independently of one another denote hydrogen or C_1 - C_4 -alkyl; or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4- $N(R^{11})$ -piperazinyl or imidazolyl group, where this group is optionally substituted by methyl or OH;

15 R^7 is hydrogen or C_1 - C_4 -alkyl;

20 R^8 represents C_1 - C_3 -alkyl, optionally substituted by NR^5R^6 ;

25 R^9 and R^{10} together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4- $N(R^{12})$ -piperazinyl group, where this group is optionally substituted by C_1 - C_4 -alkyl, C_1 - C_3 -alkoxy, $NR^{13}R^{14}$ or $CONR^{13}R^{14}$;

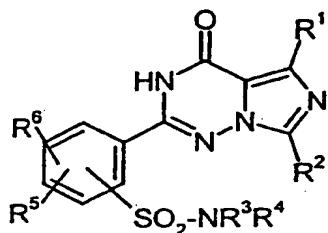
30 R^{11} denotes hydrogen, C_1 - C_3 -alkyl, optionally substituted by phenyl; (hydroxy)- C_2 - C_3 -alkyl; or C_1 - C_4 -alkanoyl;

R^{12} is hydrogen, C_1 - C_6 -alkyl, (C_1 - C_3 -alkoxy)- C_2 - C_6 -alkyl; (hydroxy)- C_2 - C_6 -alkyl; ($R^{13}R^{14}N$)- C_2 - C_6 -alkyl; ($R^{13}R^{14}NOC$)- C_1 - C_6 -alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$, or $C(NH)NR^{13}R^{14}$; and

R^{13} and R^{14} each independently of one another represent hydrogen; C_1 - C_4 -alkyl; (C_1 - C_3 -alkoxy)- C_2 - C_4 -alkyl; or (hydroxy)- C_2 - C_4 -alkyl,

and their respective salts, hydrates, alkoxides and tautomers.

12. The combination preparation as claimed in any of claims 1 to 10,
5 characterized in that the PDE inhibitor (active compound component A) is a
cGMP PDE inhibitor and is in particular selected from the group consisting
of 2-phenyl-substituted imidazotiazinones of the general formula



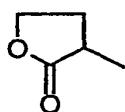
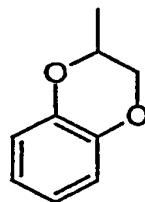
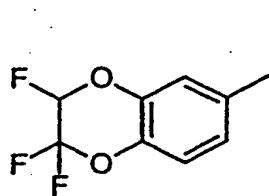
in which

10 R^1 represents hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms;

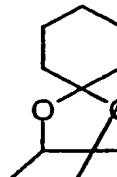
15 R^2 represents straight-chain alkyl having up to 4 carbon atoms;

20 R^3 and R^4 are identical or different and represent hydrogen or represent straight-chain or branched alkenyl or alkoxy having in each case up to 8 carbon atoms, or

25 represent a straight-chain or branched alkyl chain having up to 10 carbon atoms which is optionally interrupted by an oxygen atom and which is optionally mono- to polysubstituted by identical or different substituents from the group consisting of trifluoromethyl, trifluoromethoxy, hydroxyl, halogen, carboxyl, benzyloxycarbonyl, straight-chain or branched alkoxycarbonyl having up to 6 carbon atoms and/or by radicals of the formulae $-SO_3H$, $-(A)_a-NR^7R^8$, $-O-CO-NR^7R^8$, $-S(O)_b-R^9$, $-P(O)(OR^{10})(OR^{11})$,



and/or



in which

a and b are identical or different and represent a number 0 or 1,

5

A represents a radical CO or SO₂,

R⁷, R^{7'}, R⁸ and R^{8'} are identical or different and represent hydrogen, or represent cycloalkyl having 3 to 8 carbon atoms, aryl having 6 to 10 carbon atoms, a 5- to 6-membered unsaturated, partially unsaturated or saturated optionally benzo-fused heterocycle having up to 3 heteroatoms from the group consisting of S, N and O, where the abovementioned ring systems are optionally mono- to polysubstituted by identical or different substituents from the group consisting of hydroxyl, nitro, trifluoromethyl, trifluoromethoxy, carboxyl, halogen, straight-chain or branched alkoxy or alkoxy carbonyl having in each case up to 6 carbon atoms or by a group of the formula -(SO₂)_cNR¹²R¹³,

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in which

c represents a number 0 or 1,

R¹² and R¹³ are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms,

5

or

R⁷, R^{7'}, R⁸ and R^{8'} represent straight-chain or branched alkoxy having up to 6 carbon atoms, or

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represent straight-chain or branched alkyl having up to 8 carbon atoms which is optionally mono- or polysubstituted by identical or different substituents from the group consisting of hydroxyl, halogen, aryl having 6 to 10 carbon atoms, straight-chain or branched alkoxy or alkoxy carbonyl having in each case up to 6 carbon atoms, or by a group of the formula -(CO)_d-NR¹⁴R¹⁵,

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in which

R¹⁴ and R¹⁵ are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

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and

d represents a number 0 or 1,

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or

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R⁷ and R⁸ and/or R^{7'} and R^{8'} together with the nitrogen atom form a 5- to 7-membered saturated heterocycle which may optionally contain a further heteroatom from the group consisting of S and O or a radical of the formula -NR¹⁶,

in which

5 R¹⁶ represents hydrogen, aryl having 6 to 10 carbon atoms, benzyl, a 5- to 7-membered aromatic or saturated heterocycle having up to 3 heteroatoms from the group consisting of S, N and O, which heterocycle is optionally substituted by methyl, or represents straight-chain or branched alkyl having up to 6 carbon atoms which is optionally substituted by hydroxyl,

10 R⁹ represents aryl having 6 to 10 carbon atoms, or represents straight-chain or branched alkyl having up to 4 carbon atoms,

15 R¹⁰ and R¹¹ are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

20 and/or the alkyl chain listed above under R³/R⁴ is optionally substituted by cycloalkyl having 3 to 8 carbon atoms, aryl having 6 to 10 carbon atoms or by a 5- to 7-membered partially unsaturated, saturated or unsaturated optionally benzo-fused heterocycle which may contain up to 4 heteroatoms from the group consisting of S, N; O or a radical of the formula -NR¹⁷, in which

25 R¹⁷ represents hydrogen, hydroxyl, formyl, trifluoromethyl, straight-chain or branched acyl or alkoxy having in each case up to 4 carbon atoms, or represents straight-chain or branched alkyl having up to 6 carbon atoms which is optionally mono- to polysubstituted by identical or different substituents from the group consisting of hydroxyl and straight-chain or branched alkoxy having up to 6 carbon atoms,

30 and where aryl and the heterocycle are optionally mono- to polysubstituted by identical or different substituents from the group consisting of nitro, halogen, -SO₃H, straight-chain or branched alkyl or alkoxy having in each case up to 6 carbon atoms, hydroxyl, trifluoromethyl, trifluoromethoxy and/or by a radical

of the formula $-\text{SO}_2\text{NR}^{18}\text{R}^{19}$,

in which

5 R^{18} and R^{19} are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,

and/or

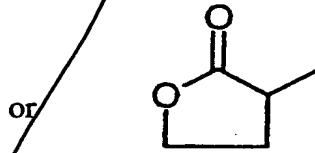
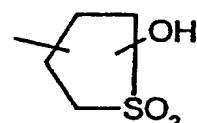
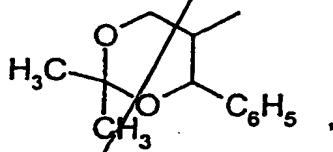
10 R^3 or R^4 represent a group of the formula $-\text{NR}^{20}\text{R}^{21}$,

in which

15 R^{20} and R^{21} have the meaning of R^{18} and R^{19} given above and are identical to or different from this meaning

and/or

20 R^3 or R^4 represent adamantly, or represent radicals of the formulae



25 or represent cycloalkyl having 3 to 8 carbon atoms, aryl having 6 to 10 carbon atoms or represent a 5- to 7-membered partially unsaturated, saturated or unsaturated optionally benzo-fused

heterocycle which may contain up to 4 heteroatoms from the group consisting of S, N; O or a radical of the formula -NR²²,

in which

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R²² has the meaning of R¹⁶ given above and is identical to or different from this meaning, or
represents carboxyl, formyl or straight-chain or branched acyl having up to 5 carbon atoms,

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and where cycloalkyl, aryl and/or the heterocycle are optionally mono- to polysubstituted by identical or different substituents from the group consisting of halogen, triazolyl, trifluoromethyl, trifluoromethoxy, carboxyl, straight-chain or branched acyl or alkoxy carbonyl having in each case up to 6 carbon atoms, nitro, and/or by groups of the formulae -SO₃H, -OR²³, (SO₂)_eNR²⁴R²⁵, -P(O)(OR²⁶)(OR²⁷),

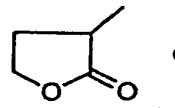
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in which

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e represents a number 0 or 1,

R²³ represents a radical of the formula



or

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represents cycloalkyl having 3 to 7 carbon atoms, or

represents hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms which is optionally substituted by cycloalkyl having 3 to 7 carbon atoms, benzyloxy, tetrahydropyranyl, tetrahydrofuranyl, straight-chain or branched alkoxy or alkoxy carbonyl having in each case up to 6 carbon atoms, carboxyl, benzyloxycarbonyl or phenyl which for its part may be mono- to polysubstituted by identical or

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different substituents from the group consisting of straight-chain or branched alkoxy having up to 4 carbon atoms, hydroxyl and halogen,

5 and/or alkyl is optionally substituted by radicals of the formulae -CO-NR²⁸R²⁹ or -CO-R³⁰,

in which

10 R²⁸ and R²⁹ are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 8 carbon atoms, or

15 R²⁸ and R²⁹ together with the nitrogen atom form a 5- to 7-membered saturated heterocycle which may optionally contain a further heteroatom from the group consisting of S and O,

and

20 R³⁰ represents phenyl or adamantyl,

25 R²⁴ and R²⁵ have the meaning of R¹⁸ and R¹⁹ given above and are identical to or different from this meaning,

30 R²⁶ and R²⁷ have the meaning of R¹⁰ and R¹¹ given above and are identical to or different from this meaning

and/or cycloalkyl, aryl and/or the heterocycle are optionally substituted by straight-chain or branched alkyl having up to 6 carbon atoms which is optionally substituted by hydroxyl, carboxyl, by a 5- to 7-membered heterocycle having up to 3 heteroatoms from the group consisting of S, N and O or by groups of the formula -SO₂-R³¹, P(O)(OR³²)(OR³³) or -NR³⁴R³⁵,

in which

R^{31} is hydrogen or has the meaning of R^9 given above and is identical to or different from this meaning,

5 R^{32} and R^{33} have the meaning of R^{10} and R^{11} given above and are identical to or different from this meaning,

10 R^{34} and R^{35} are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms which is optionally substituted by hydroxyl or straight-chain or branched alkoxy having up to 4 carbon atoms, or

15 R^{34} and R^{35} together with the nitrogen atom form a 5- to 6-membered saturated heterocycle which may contain a further heteroatom from the group consisting of S and O or a radical of the formula $-NR^{36}$,

in which

20 R^{36} represents hydrogen, hydroxyl, straight-chain or branched alkoxy carbonyl having up to 7 carbon atoms or straight-chain or branched alkyl having up to 5 carbon atoms which is optionally substituted by hydroxyl,

or

25 R^3 and R^4 together with the nitrogen atom form a 5- to 7-membered unsaturated or saturated or partially unsaturated optionally benzofused heterocycle which may optionally contain up to 3 heteroatoms from the group consisting of S, N, O or a radical of the formula $-NR^{37}$,

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in which

R^{37} represents hydrogen, hydroxyl, formyl, trifluoromethyl, straight-chain

or branched acyl, alkoxy or alkoxy carbonyl having in each case up to 4 carbon atoms,

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or represents straight-chain or branched alkyl having up to 6 carbon atoms which is optionally mono- to polysubstituted by identical or different substituents from the group consisting of hydroxyl, trifluoromethyl, carboxyl, straight-chain or branched alkoxy or alkoxy carbonyl having in each case up to 6 carbon atoms or by groups of the formula - (D)_f-NR³⁸R³⁹, -CO-(CH₂)_g-O-CO-R⁴⁰, -CO-(CH₂)_h-OR⁴¹ or -P(O)(OR⁴²)(OR⁴³),

10

in which

g and h are identical or different and represent a number 1, 2, 3 or 4.

15

and

f represents a number 0 or 1.

D represents a group of the formula -CO or -SO₂.

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R^{38} and R^{39} are identical or different and have the meaning of R^7 and R^8 given above,

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R^{40} represents straight-chain or branched alkyl having up to 6 carbon atoms.

R^{41} represents straight-chain or branched alkyl having up to 6 carbon atoms.

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R^{42} and R^{43} are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms.

or

R^{37} represents a radical of the formula $-(CO)_i-E$,

in which

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i represents a number 0 or 1,

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E represents cycloalkyl having 3 to 7 carbon atoms or benzyl,
represents aryl having 6 to 10 carbon atoms or a 5- to 6-
membered aromatic heterocycle having up to 4 heteroatoms
from the group consisting of S, N and O, where the ring
systems listed above are optionally mono- to polysubstituted
by identical or different substituents from the group consisting
of nitro, halogen, $-SO_3H$, straight-chain or branched alkoxy
having up to 6 carbon atoms, hydroxyl, trifluoromethyl,
trifluoromethoxy or by a radical of the formula $-SO_2-NR^{44}R^{45}$,

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in which

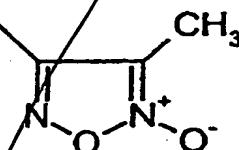
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R^{44} and R^{45} have the meaning of R^{18} and R^{19} given above and
are identical to or different from this meaning,

or

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E represents radicals of the formulae



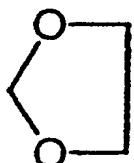
or



and the heterocycle listed under R^3 and R^4 , which is formed together

with the nitrogen atom, is optionally mono- to polysubstituted by identical or different substituents, if appropriate also geminally, by hydroxyl, formyl, carboxyl, straight-chain or branched acyl or alkoxy carbonyl having in each case up to 6 carbon atoms, nitro and groups of the formulae $-P(O)(OR^{46})(OR^{47})$,

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 $=NR^{48}$ or $-(CO)_jNR^{49}R^{50}$,

in which

R^{46} and R^{47} have the meaning of R^{10} and R^{11} given above and are identical to or different from this meaning,

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R^{48} is hydroxyl or straight-chain or branched alkoxy having up to 4 carbon atoms,

15 j is a number 0 or 1,

and

R^{49} and R^{50} are identical or different and have the meaning of R^{14} and R^{15} given above,

20

and/or the heterocycle listed under R^3 and R^4 , which is formed together with the nitrogen atom, is optionally substituted by straight-chain or branched alkyl having up to 6 carbon atoms which is optionally mono- to polysubstituted by identical or different substituents from the group consisting of hydroxyl, halogen, carboxyl, cycloalkyl or cycloalkyloxy having in each case 3 to 8 carbon atoms, straight-chain or branched alkoxy or alkoxy carbonyl having in each case up to 6 carbon atoms or by a radical of the formula $-SO_3H$, $-NR^{51}R^{52}$ or $P(O)OR^{53}OR^{54}$,

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in which

5 R^{51} and R^{52} are identical or different and represent hydrogen, phenyl, carboxyl, benzyl or straight-chain or branched alkyl or alkoxy having in each case up to 6 carbon atoms,

10 R^{53} and R^{54} are identical or different and have the meaning of R^{10} and R^{11} given above,

15 and/or the alkyl is optionally substituted by aryl having 6 to 10 carbon atoms which for its part may be mono- to polysubstituted by identical or different substituents from the group consisting of halogen, hydroxyl, straight-chain or branched alkoxy having up to 6 carbon atoms, or by a group of the formula $-NR^{51}R^{52}$,

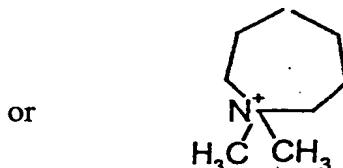
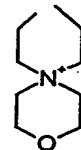
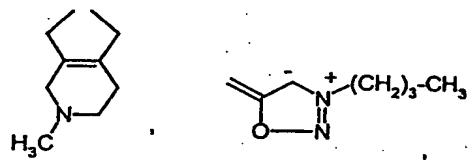
in which

20 $R^{51'}$ and $R^{52'}$ have the meaning of R^{51} and R^{52} given above and are identical to or different from this meaning,

25 and/or the heterocycle listed under R^3 and R^4 , which is formed together with the nitrogen atom, is optionally substituted by aryl having 6 to 10 carbon atoms or by a 5- to 7-membered saturated, partially unsaturated or unsaturated heterocycle having up to 3 heteroatoms from the group consisting of S, N and O, if appropriate also attached via an N-function, where the ring systems for their part may be substituted by hydroxyl or by straight-chain or branched alkyl or alkoxy having in each case up to 6 carbon atoms,

30 or

R^3 and R^4 together with the nitrogen atom form radicals of the formulae



R^5 and R^6 are identical or different and represent hydrogen, straight-chain or branched alkyl having up to 6 carbon atoms, hydroxyl or represent straight-chain or branched alkoxy having up to 6 carbon atoms.

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and their respective salts, hydrates, alkoxides and tautomers.

13. The combination preparation as claimed in any of claims 1 to 10, characterized in that the PDE inhibitor (active compound component A) is a cGMP PDE inhibitor and in particular is selected from the group consisting of (a)

10 (a) 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulfonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]-pyrimidin-7-one (sildenafil) and its salts, hydrates, alkoxides and tautomers; and (b) 2-[2-ethoxy-5-(4-ethylpiperazine-1-sulfonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f]-[1,2,4]-triazin-4-one and its salts, hydrates, alkoxides and tautomers.

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14. The combination preparation as claimed in claim 13, in that the PDE inhibitor (active compound component A) is 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulfonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]-pyrimidin-7-one citrate (sildenafil citrate, ViagraTM) or 2-[2-ethoxy-5-(4-ethylpiperazine-1-sulfonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one hydrochloride trihydrate.

15. The use of antilipemics for enhancing the activity of PDE inhibitors, in

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particular cGMP PDE inhibitors.

16. The use as claimed in claim 15 in the treatment of sexual dysfunction in men and women, in particular in the treatment of erectile dysfunction.

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17. The use as claimed in claim 15 or 16, characterized in that the antilipemic and the PDE inhibitor are used either simultaneously or else successively.

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18. The use as claimed in any of claims 15 to 17, characterized in that the antilipemic and the PDE inhibitor are present as a functional unit, in particular in the form of a mixture, a mix or a blend.

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19. The use as claimed in any of claims 15 to 17, characterized in that the antilipemic and the PDE inhibitor are present (spatially) separated, in particular as a kit-of-parts.

20. The use as claimed in any of claims 15 to 19, characterized in that the antilipemic is selected from the compounds defined in claims 7 to 10.

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21. The use as claimed in any of claims 15 to 20, characterized in that the PDE inhibitor is selected from the compounds defined in claims 11 to 14.

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